711017 (3/12/85)
Hamashima Cont. of 656731
JOP 10/4/83

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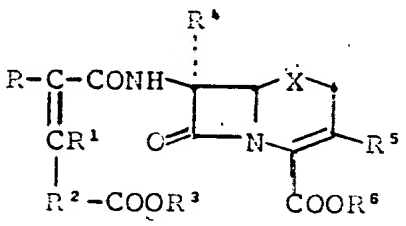
WHAT WE CLAIM IS:

1. A 7beta-(carboxyalkenoylamino)-3-cephem-4-carboxylic acid compound represented by following formula and its derivatives:



514/202, 203, 204
544/16, 22, 25, 27, 28

(wherein R is aryl or a heterocyclic group;
R^1 is hydrogen or halogen;
R^2 is a single bond, alkylene, or thiaalkylene;
R^3 is a hydrogen atom, salt forming atom or group, or ester forming group;
R^4 is hydrogen or methoxy;
R^5 is hydrogen or a 3-substituent of cephalosporins;
R^6 is a hydrogen atom, salt forming atom or group, or ester forming group; and
X is oxygen, sulfur, or sulfinyl,
with the proviso that when R^2 is thiaalkylene, R^1 is halogen).

2. A compound claimed in Claim 1 wherein 7-acylamido double bond has amido and carboxylic substituents in cis position.

3. A compound claimed in Claim 1 wherein R is phenyl, furyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, or thiadiazolyl, especially that wherein R is optionally protected aminoisoxazolyl, aminothiazolyl, or aminothiadiazolyl.

4. A compound as claimed in Claim 1 wherein R is optionally

CLAIM 1

protected aminothiazolyl.

5. A compound as claimed in Claim 1 wherein R^1 is hydrogen or chlorine.

6. A compound as claimed in Claim 1 wherein R^2 is optionally branched 1 to 3C alkylene.

7. A compound as claimed in Claim 1 wherein R^4 is hydrogen.

8. A compound as claimed in Claim 1 wherein R^5 is hydrogen, vinyl, cyanovinyl, trifluoropropenyl, acetoxymethyl, carbamoyloxymethyl, triazolylthiomethyl, methyltetrazolylthiomethyl, or thiadiazolylthiomethyl optionally substituted by amino, aminomethyl, or methyl.

9. A compound as claimed in Claim 1 wherein R^3 and/or R^6 is hydrogen, alkali metal, or a pharmaceutically acceptable ester group.

10. A compound as claimed in Claim 1 wherein R^3 and/or R^6 is an alkyl or aralkyl ester-forming group.

11. A compound as claimed in Claim 1 wherein X is sulfur.

12. A compound as claimed in Claim 1 that is one selected from the group consisting of :

7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-cephem-4-carboxylic acid,

7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-methyl-3-cephem-4-carboxylic acid,

7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-vinyl-3-cephem-4-carboxylic acid,

7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-trifluoropropenyl-3-cephem-4-carboxylic acid,

7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-acetoxymethyl-3-cephem-4-carboxylic acid,

7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-carbamoyloxymethyl-3-cephem-4-carboxylic acid,

7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-methoxymethyl-3-cephem-4-carboxylic acid,

7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-methylthiomethyl-3-cephem-4-carboxylic acid,

7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-cyanomethylthiomethyl-3-cephem-4-carboxylic acid,

7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-pyridinioethyl-3-cephem-4-carboxylate,

7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-triazolylthiomethyl-3-cephem-4-carboxylic acid,

7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-thiadiazolylthiomethyl-3-cephem-4-carboxylic acid,

7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-methyltetrazolylthiomethyl-3-cephem-4-carboxylic acid,

7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-methoxy-3-cephem-4-carboxylic acid,

7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-chloro-3-cephem-4-carboxylic acid,

7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-

3-fluoroethylthio-3-cephem-4-carboxylic acid,

7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-trifluoroethylthio-3-cephem-4-carboxylic acid,

7beta-[2-(2-aminothiazol-4-yl)-5-carboxy-2-pentenoylamino]-3-cephem-4-carboxylic acid,

7beta-[2-(2-aminothiazol-4-yl)-6-carboxy-2-hexenoylamino]-3-cephem-4-carboxylic acid,

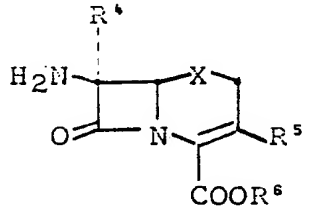
7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-2-pentenoylamino]-3-cephem-4-carboxylic acid,

7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-4-methyl-2-pentenoylamino]-3-cephem-4-carboxylic acid, and

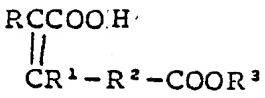
7beta-[2-(2-aminothiazol-4-yl)-4-carboxy-3-chloro-2-butenoylamino]-3-cephem-4-carboxylic acid.

and its salt and esters.

13. A process for preparing a compound as claimed in Claim 1 which comprises amidating 7beta-amino-3-cephem-4-carboxylic acid derivative represented by the following formula:

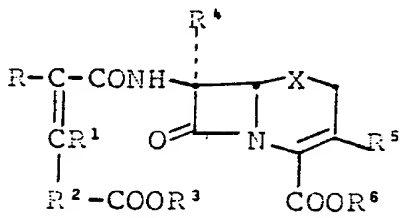


(wherein R^4, R^5, R^6, and X are as defined in Claim 1) or its reactive derivative with carboxyalkenoic acid represented by the following formula:



(wherein R, R^1, R^2, and R^3 are as defined in Claim 1) or its reactive derivative.

14. A process for preparing a salt as claimed in Claim 1 which comprises neutralizing a 7beta-(carboxyalkenoylamino)-3-cephem-4-carboxylic acid represented by the following formula:

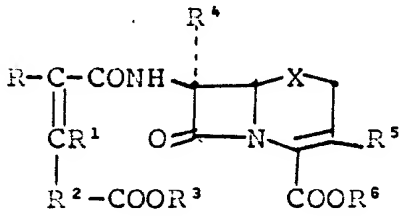


(wherein R, R^1, R^2, R^3, R^4, R^5, R^6, and X are as defined in Claim 1 provided that at least one of R^3 and R^6 are hydrogen) or its reactive derivative with a base.

15. A process for preparing a compound as claimed in Claim 1 which comprises introducing a 3-function in a conventional manner selected from 3-double bond introduction by basic or thermal elimination of the corresponding 3-(hydroxy, acyloxy, or halo)cepham, sulfoxide reduction, reduction of 3-(halo or 3-sulfonyloxy)cephem, and displacement of 3-(leaving group-substituted)methyl-3-cephem with the corresponding nucleophilic reagent.

16. A process for preparing a compound as claimed in Claim 1 which comprises deprotecting a protected amino or protected carboxy of protected 7beta-(carboxyalkenoylamino)-3-cephem-

4-carboxylic acid represented by the following formula:

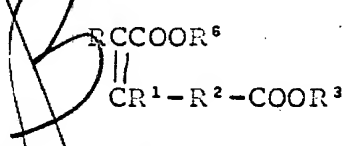


(wherein R, R^1, R^2, R^3, R^4, R^6, and X are as defined in Claim 1 provided that at least one of R, R^3, R^5, and R^5 is protected) or its reactive derivative in a conventional manner.

17. An antibacterial composition comprising an effective amount of the compound as claimed in Claim 9 and conventional carrier.

18. A method for combating bacteria which comprises bringing an effective amount of the compound as claimed in Claim 9 to contact with the bacteria.

19. A compound represented by the following formula:



(wherein R, R^1, R^2, R^3, and R^6, are as defined in Claim 1).

20. A compound claimed in Claim 19 wherein R is amino-thiazolyl optionally protected by benzyloxycarbonyl, t-butoxy-carbonyl, methylbenzyloxycarbonyl formyl, chloroacetyl, or benzal.

21. A compound as claimed in Claim 19 wherein R^1 is hydrogen.

22. A compound as claimed in Claim 19 wherein R^2 is 1 to 3C

optionally branched alkylene.

23. A compound as claimed in Claim 22 wherein R^2 is methylene.

24. A compound as claimed in Claim 19 wherein R^3 is hydrogen, methyl, t-butyl, benzyl, methylbenzyl, p-methoxybenzyl, or p-nitrobenzyl.

25. A compound as claimed in Claim 19 wherein R^6 is hydrogen, diphenylmethyl, or p-methoxybenzyl.

26. A process for preparing a compound as claimed in Claim 19, which comprises subjecting an oxalate of the following formula:

$$R\text{-}CO\text{-}COOR^6$$

(wherein R and R^6 are as defined in Claim 1)
to the Wittig type reaction by treating with an alkylidenephosphorane of the following formula:

$$Ar_3P{=}CR^1\text{-}R^2\text{-}COOR^3$$

(wherein R^1, R^2, and R^3 are as defined in Claim 1 and Ar is aryl)
in an inert solvent at 50°C to 120°C for 10 minutes to 10 hours.

27. A process for preparing a compound as claimed in Claim 19, which comprises subjecting a formyl oxalate of the following formula:

$$R\text{-}\underset{\displaystyle CHO}{\underset{|}{CH}}\text{-}COOR^6$$

(wherein R and R^6 are as defined in Claim 1)
or its acetal to the Wittig type reaction by treating with an alkylidenephosphorane of the following formula:

$$Ar_3P{=}CH\text{-}R^{20}\text{-}COOR^3$$

(wherein Ar and R^3 are as defined in Claim 26, and R^{20} is a single bond or 1 to 3C alkylene)
in an inert solvent at 50°C to 120°C for 10 minutes to 10 hours.

28. A process for preparing a compound as claimed in Claim 19, which comprises deprotecting the carboxy-protecting group R^3 or R^6 to give a compound of the following formula:

$$\begin{array}{l} R\text{-}C\text{-}COOR^6 \\ \quad\| \\ \quad CR^1\text{-}R^2\text{-}COOR^3 \end{array}$$

(wherein R, R^1, R^2 are as defined in Claim 1, and one or both of R^3 and R^6 are hydrogen)
by treating with acid, Lewis acid and cation scavenger, base, or hydrogen and catalyst in an inert solvent at -50°C to 100°C for 1/6 to 10 hours.